tered to remove cyanoacetamide (1.24 g., 74%, m.p. 114–117°, m.m.p. 117–120°). The filtrate was distilled giving benzyl bromide (3.37 g., 98%, b.p. 60° at 3.5 mm.). The residue gave 5.9 g. of crude triphenylphosphine oxide (m.p. 70–120°) which was washed with 5 ml. of ether and with 5 ml. of water giving 4.87 g. of pure triphenyl phosphine oxide, m.p. 149–152°.

Oxidation of Phosphites or Phosphines by Means of Monobromocyanoacetamide and Allyl Alcohol.—To a solution of monobromocyanoacetamide (1.63 g., 0.01 mole) and allyl alcohol (0.6 g., 0.011 mole) in 20 ml. of ether was added dropwise with vigorous stirring a solution of tri-*n*-butyl phosphite (2.60 g., 0.01 mole) in 10 ml. of ether at room temperature. A white precipitate, cyanoacetamide, soon appeared. The mixture was kept standing overnight at room temperature and was filtered to remove cyanoacetamide (0.51 g., 61%). After removal of ether from the filtrate, allyl bromide (0.67 g., 55%, b.p. 72–76°) and tri-*n*-butyl phosphate (1.90 g., 72%, b.p. 110–120° at 0.45 mm.) were obtained by fractionation. Similarly, various phosphates and phosphine oxides were obtained from the corresponding phosphites or phosphines (see Table II).

Oxidation of Triphenyl Phosphine by Means of Monobromocyanoacetamide and Allyl Alcohol.—A solution of triphenyl phosphine (2.62 g., 0.01 mole) in 25 ml. of chloroform was added dropwise to a suspension of monobromocyanoacetamide (1.63 g., 0.01 mole) and allyl alcohol (1.04 g., 0.02 mole) in 15 ml. of chloroform with vigorous stirring at room temperature. The reaction started soon with liberation of heat. After standing overnight, the mixture was filtered to remove cyanoacetamide (0.73 g., 87%, m.p. 107–113°) and from the filtrate, allyl bromide (10%, b.p. 71–72°) was obtained. The residue solidified soon and gave triphenyl phosphine oxide (2.23 g., 80%, m.p. 145–150°).

Oxidation of Alkyl Propylene Phosphites by Means of Monobromocyanoacetamide and Benzyl Alcohol.—A solution of ethyl propylene phosphite (1.50 g., 0.01 mole) in 10 ml. of ether was added dropwise to a suspension of monobromocyanoacetamide (1.63 g., 0.01 mole) and benzyl alcohol (1.10 g., 0.01 mole) in ether with vigorous stirring at room temperature. The reaction proceeded with liberation of heat and a white precipitate, cyanoacetamide, appeared soon. After standing overnight at room temperature, the mixture was filtered to remove cyanoacetamide (0.80 g., 95%). After removal of ether from the filtrate, benzyl bromide (1.54 g., 90%) and ethyl propylene phosphate (1.13 g., 68%, b.p. 120–128° at 4–5 mm., lit.[13] b.p. 105–108° at 3 mm.) were obtained by fractionation.

Anal. Calcd. for $C_5H_{11}O_4P$: C, 36.15; H, 6.67. Found: C, 36.62; H, 7.13.

Similarly, propyl propylene phosphate and butyl propylene phosphate were prepared from the corresponding cyclic phosphites (see Table III).

Oxidation of Ethyl Ethylene Phosphite by Means of Monobromocyanoacetamide and Benzyl Alcohol.—A solution of ethyl ethylene phosphite (1.40 g., 0.01 mole) in 10 ml. of ether was added dropwise to a suspension of monobromocyanoacetamide (1.63 g., 0.01 mole) and benzyl alcohol (1.10 g., 0.01 mole) with vigorous stirring at room temperature. Since a viscous, oily product was formed during the addition of the phosphite, 20 ml. of THF was added to dissolve it. After standing overnight, the solvent was removed and the residue was filtered to remove cyanoacetamide (95%). From the filtrate, benzyl bromide (0.95 g., 56%, b.p. 55–56° at 2.5 mm.) and ethyl ethylene phosphate (0.55 g., 36%, b.p. 72–75° at 0.004 mm.) were obtained by fractionation.

Oxidation of Diethyl Phosphite by Means of Monobromocyanoacetamide and Benzyl Alcohol.—A solution of diethyl phosphite (1.40 g., 0.01 mole) in 10 ml. of THF was added dropwise to a solution of monobromocyanoacetamide (1.63 g., 0.01 mole) and benzyl alcohol (1.10 g., 0.01 mole) in 20 ml. of THF at room temperature. After standing overnight at room temperature, the mixture was filtered to remove cyanoacetamide (0.74 g., 94%). The filtrate was distilled giving benzyl bromide (1.71 g., 100%) and diethyl hydrogen phosphate (1.47 g., 96%, b.p. 113–115° at 0.025 mm.). Diethyl hydrogen phosphate was identified by paper chromatography, R_f 0.70 (solvent system: *n*-propyl alcohol–concentrated NH_4OH–water, 6:3:1).

Acknowledgment.—The authors wish to express their hearty thanks to Dr. Tsujiaki Hata and Dr. Hiroyuki Nohira for helpful discussions and to Miss Toshiko Aoyagi for her microanalyses.

(13) B. A. Arbuzov, K. V. N. Konorov, and Z. G. Shishova, *Izv. Akad. Nauk SSSR Otd. Khim. Nauk*, 823 (1954); *Chem. Abstr.*, **49**, 13,891 (1954).

Yohimbane Derivatives. I. The Preparation of 3-Substituted Yohimbane Derivatives

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The preparation of 3-cyano-, 3-methyl-, 3-phenyl-, and 3-benzylyohimbanes is described. 3-Dehydroyohimbane salts (II) react with cyanide to give 3-cyanoyohimbanes (I). Compounds I or II treated with methyllithium or phenyllithium gave the corresponding 3-methyl- and 3-phenylyohimbanes (III); benzylmagnesium bromide gave 3-benzylyohimbane. Oppenauer oxidation of 3-methyl-17β-hydroxyyohimbane (IIIc) and 3,16α-dimethyl-17α-hydroxyyohimbane (IIId) gave, respectively, 3-methylyohimbone (IVa) and 3,16α-dimethylyohimbone (IVb). The position of substitution was supported by the n.m.r. spectra and by failure to give 3-dehydroyohimbanes when oxidized with *t*-butyl hypochlorite. The stereochemistry at C-3 was not firmly established since the rotation data tended to support the α-configuration but the infrared data were inconclusive. The infrared spectrum of 3-dehydroyohimbane base (Va) showed a strong NH band which led us to propose a different structure from that reported in the literature.

Of the many investigations in the field of the yohimbanoid[1] alkaloids which have been reported in recent years, a considerable number have concerned themselves with the chemistry of the C-3 position.[2] These studies have included acid-[3,4] and base-catalyzed[4,5] epimerizations, oxidative rearrangements,[6] and spectral correlations.[2a,7] Convenient methods have been devised for the oxidation of yohimbanoids[1] to give 3-dehydroyohimbanoids[8–10] and the latter have been re-

(1) In this paper, the term "yohimbanoids" refers to the pentacyclic skeleton without regard to the stereochemistry of the ring junctions whereas "yohimbanes" refers to compounds having the normal or all *trans* configuration which is present in yohimbine.

(2) Much of this work is reviewed in the following articles: (a) E. Wenkert and D. K. Roychaudhuri, *J. Am. Chem. Soc.*, **80**, 1613 (1958); (b) P. E. Aldrich, *et al.*, *ibid.*, **81**, 2481 (1959).

(3) R. E. Woodson, Jr., H. W. Youngken, E. Schlittler, and J. A. Schneider, "Rauwolfia," Little, Brown and Co., Boston, Mass., 1957, p. 85.

(4) E. Wenkert and L. H. Liu, *Experientia*, **11**, 302 (1955).

(5) M. Janot, R. Goutarel, A. le Hir, M. Amin, and V. Prelog, *Bull. soc. chim. France*, 1085 (1952).

(6) (a) J. Shavel, Jr., and H. Zinnes, *J. Am. Chem. Soc.*, **84**, 1320 (1962); (b) N. Finch and W. I. Taylor, *ibid.*, **84**, 1318, 3871 (1962); (c) N. Finch, C. W. Gemenden, I. H. Hsu, and W. I. Taylor, *ibid.*, **85**, 1520 (1963).

(7) W. E. Rosen, *Tetrahedron Letters*, 481 (1961).

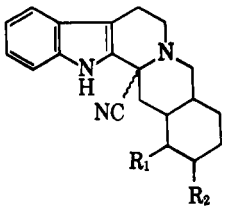
(8) F. L. Weisenborn and P. A. Diassi, *J. Am. Chem. Soc.*, **78**, 2022 (1956).

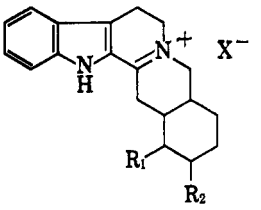
(9) E. Wenkert and D. K. Roychaudhuri, *J. Org. Chem.*, **21**, 1315 (1956).

(10) W. O. Godtfredsen and S. Vangedal, *Acta Chem. Scand.*, **10**, 1414 (1956).

duced[8-12] by various methods to yield predominately one or a mixture of both of the possible C-3 epimers. No one has reported the synthesis of 3-alkyl, 3-aryl, or 3-aralkyl yohimbanoid derivatives. As part of a general program to modify the yohimbane nucleus chemically, we have introduced methyl, phenyl, and benzyl groups into the C-3 position.

Our synthetic method was modeled after that described by Leonard and co-workers[13] for the preparation of 10-alkyl- and 10-aralkylquinolizidines. 3-Cyanoyohimbane (Ia) and 3-cyanoyohimbine (Ib) were nearly quantitatively precipitated when an aqueous methanolic solution of 3-dehydroyohimbane chloride[14] (IIa) or 3-dehydroyohimbine chloride[14] (IIb) was treated with potassium cyanide.[15,16] These compounds have a weak but distinct cyano band at 2300 cm.$^{-1}$ and are distinguished from the 3-dehydro bases V in that they lack the characteristic band at 1636 cm.$^{-1}$. As shown by the ultraviolet spectra, they lose HCN in



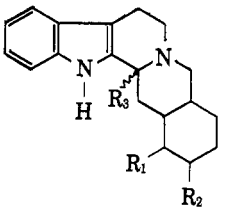


Ia, R_1 = H; R_2 = H
b, R_1 = α-CO_2CH_3; R_2 = α-OH

IIa, R_1 = H; R_2 = H
b, R_1 = α-CO_2CH_3; R_2 = α-OH
c, R_1 = H; R_2 = β-OH
d, R_1 = α-CH_3; R_2 = α-OH

acid or base to regenerate the corresponding 3-dehydroyohimbanes. In ordinary spectral grade ethanol, which is slightly acidic, the spectrum suggested the presence of both 3-dehydro salt II and a compound having the typical 2,3-dialkylindole chromophore, whereas in ethanol to which hydrochloric acid had been added, the spectrum was that of a pure 3-dehydro salt; in ethanol which had been neutralized by the addition of a few drops of aqueous sodium hydroxide, the spectrum was indistinguishable from that of a pure 3-dehydro base (V). When determined in acetonitrile, the spectrum resembled that of a 2,3-dialkylindole such as yohimbane[17] except that it also contained additional broad maxima at 305–312 and 318 mμ. Since 3-dehydro bases have strong absorption in these regions, it is apparent that some loss of HCN took place in acetonitrile.[18] The ease of preparation of the 3-cyanoyohimbanes is no doubt dependent on their immediate precipitation on formation.[19] Of practical importance in their use as intermediates is the fact that, in contrast to the dehydro salts, they have considerable solubility in ether and benzene.

The reaction of Ia with an excess of methyllithium gave the desired 3-methylyohimbane (IIIa) in 41% yield, whereas 3-phenylyohimbane (IIIb) was isolated in 26% yield when phenyllithium was used. These same products were also obtained in yields of 25 and 21%, respectively, when an ether suspension of 3-dehydroyohimbane perchlorate[9] (IIa) was treated with the organolithium reagents. Similarly, the chlorides of 3-dehydro-17β-hydroxyyohimbane (IIc) and 3-dehydro-16α-methyl-17α-hydroxyyohimbane (IId) gave



IIIa, R_1 = H; R_2 = H; R_3 = CH_3
b, R_1 = H; R_2 = H; R_3 = C_6H_5
c, R_1 = H; R_2 = β-OH; R_3 = CH_3
d, R_1 = α-CH_3; R_2 = α-OH; R_3 = CH_3
e, R_1 = H; R_2 = H; R_3 = $C_6H_5CH_2$

the 3-methyl derivatives IIIc and IIId in 33 and 34% yields, respectively. 3-Benzylyohimbane (IIIe) was prepared in 47% yield by the interaction of benzylmagnesium chloride with 3-dehydroyohimbane chloride.[20]

The progress of these reactions was followed by working up small aliquots of the reaction mixture and subjecting the crude products to paper ionophoresis.[21] In all cases it appeared as though reaction had ceased after a given amount of 3-substituted yohimbane had formed, the ionogram showing a spot of considerable size corresponding to the 3-dehydroyohimbane. From the reaction of methyllithium with IIc there was isolated, in addition to the expected product IIIc, crystalline 3-dehydro-17β-hydroxyyohimbane base (Vb) in 25% yield. With the reactions involving the 3-dehydro salts, competition probably took place between the desired reaction and a Zerevitinov reaction in which a hydrogen from position 14 was abstracted to give the 3-dehydro base. We have shown that 3-dehydroyohimbane base (Va) and 3-dehydro-17β-hydroxyyohimbane base (Vb) do not give 3-methyl derivatives through reaction with

(11) L. Velluz, G. Muller, R. Joly, G. Nominé, J. Mathieu, A. Alais, J. Warnant, J. Valls, R. Bucourt, and J. Joly, *Bull. soc. chim. France*, 673 (1958).

(12) G. Stork and R. K. Hill, *J. Am. Chem. Soc.* **79**, 495 (1957).

(13) (a) N. J. Leonard, A. S. Hay, R. W. Fulmer, and V. W. Gash, *ibid.*, **77**, 439 (1955); (b) N. J. Leonard and A. S. Hay, *ibid.*, **78**, 1984 (1956). These workers treated 5,10-dehydroquinolizidinium salts and 10-cyanoquinolizidine with Grignard reagents and with picolyllithium.

(14) 3-Dehydroyohimbine chloride has been described by Godtfredsen and Vangedal.[10] The other dehydroyohimbane chlorides discussed herein are new compounds prepared by the same procedure.

(15) N. J. Leonard and F. P. Hauck, Jr. [*J. Am. Chem. Soc.*, **79**, 5279 (1957)], have pointed out that the reaction of cyanide ion with ternary imminium salts is a general one which is useful in characterizing this class of compound.

(16) The only hitherto reported 3-substituted yohimbanoid derivative is 3-cyanoreserpine whose melting point and optical rotation were given in a table by G. Muller and A. Alais [*Naturwiss.*, **47**, 82 (1960)]. No other information concerning the preparation and properties of the compound was given.

(17) In acetonitrile, yohimbane has λ_{max} 227 mμ (ϵ 34,750), 281 (7750), 290 sh (6500), and λ_{min} 249 mμ (ϵ 2750).

(18) The position and intensity of absorption maxima for representative 3-cyanoyohimbanes, 3-dehydro salts, and 3-dehydro bases in various solvents are given in the Experimental section.

(19) While the 3-cyanoyohimbanes could be recrystallized from polar solvents to obtain analytical samples, considerable loss of material occurred during this process.

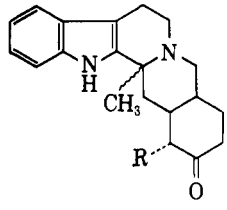
(20) This was the only instance in which an appreciable yield of 3-substituted yohimbane was obtained using a Grignard reagent. The reaction of either 3-dehydroyohimbane salts or 3-cyanoyohimbane with methylmagnesium bromide resulted in the isolation of only trace amounts of IIIa, the reaction product (after acidification) consisting almost wholly of 3-dehydroyohimbane chloride.

(21) The more basic 3-dehydroyohimbanes move faster than the 3-substituted yohimbanes. Since the electrolyte was 5 *N* acetic acid, any unreacted 3-cyanoyohimbane was detected as 3-dehydroyohimbane. The presence of 3-dehydroyohimbanes in the crude reaction products was also confirmed by the appearance of the characteristic maximum at 350 mμ in the ultraviolet spectrum determined in a solvent consisting of nine volumes of ethanol to one volume of 1 *N* aqueous hydrochloric acid.

methyllithium.[22] Whether the reactions involving 3-cyanoyohimbane (Ia) proceed by direct displacement of the cyano group or by reaction with IIa (X = CN^-), formed by prior dissociation of Ia, has not been established.

The preparation of IIIb is of particular interest since Leonard and Hay[13b] were unable to prepare 10-phenylquinolizidine by the reaction of 5,10-dehydroquinolizidinium perchlorate with phenylmagnesium bromide. Apparently the steric requirements of the phenyllithium are sufficiently satisfied so that the desired reaction can compete with the abstraction of hydrogen from position 14.[23]

3,16α-Dimethylyohimbone (IVb) was prepared in 57% yield by the Oppenauer oxidation of the corresponding alcohol IIId using aluminum phenoxide and cyclohexanone in refluxing xylene.[24] When this procedure was used for the oxidation of IIIc, considerable decomposition took place and no clean products could



IVa, R=H
b, R=CH_3

be isolated. 3-Methylyohimbone (IVa) was finally obtained in 37% yield by refluxing the same reactants in benzene for 53 hr. At the end of this period complete conversion had not occurred and 28% of the starting alcohol IIIc was recovered.

The fact that no 3-dehydroyohimbane was produced when either IIIa, IIIb, or IIIe was subjected to *t*-butyl hypochlorite oxidation followed by treatment with ethanolic hydrogen chloride lends support for the presence of the new substituent at C-3.[25] In the case of the 3-methyl derivatives, this structural assignment was confirmed by the n.m.r. spectrum which showed a sharp singlet at 1.33 p.p.m.[26] The n.m.r. spectrum also showed the absence of the C-3 hydrogen. The equatorial C-3 hydrogen of pseudoyohimbone was found to give a signal at 4.50 p.p.m.,[27,28] whereas, with yohimbane, the signal given by the axial C-3 hydrogen is part of a complex pattern between 2.42 and 3.42 p.p.m. which integrated for seven protons. The 3-methylyohimbanes gave a complex signal pattern in this region whose integration indicated only six protons. Integration of the same region in the spectrum of 3-benzylyohimbane indicated eight protons, whereas with 3-phenylyohimbane a multiplicity of signals extending from 2.42 to 3.45 p.p.m. suggested, upon integration, the presence of six protons.

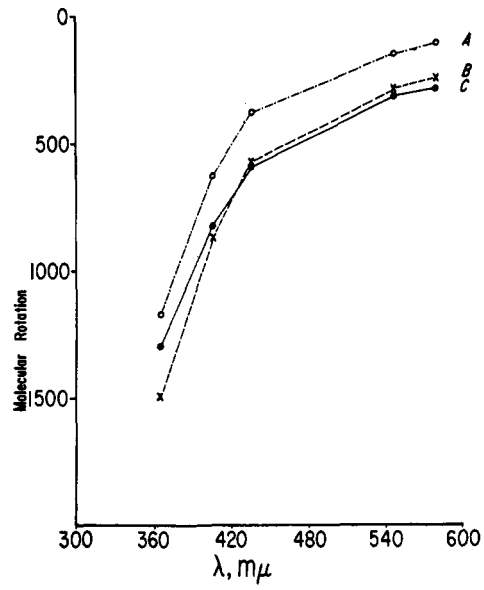


Figure 1.—Optical rotary dispersion (in chloroform) of pseudoyohimbone (A), 3-methylyohimbone (B), and yohimbone (C).

While the ultraviolet spectra of the 3-methyl and 3-benzyl derivatives were identical with those of the corresponding 3-unsubstituted analogs, the 3-phenyl group in compound IIIb was sufficiently proximate to the indole chromophore to cause the first maximum at 225 (in ethanol) to shift to 228 mμ. The effect on basicity resulting from the introduction of different types of substituents at position 3 was in the order which would be predicted from the inductive effect. 3-Methylyohimbane, yohimbane, 3-benzylyohimbane, and 3-phenylyohimbane gave respective pK_A' values of 7.93, 7.46, 6.65, and 6.40 in 70% ethanol.

The presently available data do not permit a rigorous assignment of the configuration of the C-3 substituent. While the values (Table I) of the molecular rotations of the 3-methyl derivatives, as measured at the sodium D-line wave length, lie between those of the corresponding normal (α, axial H; *trans*-quinolizidine) and pseudo (β, equatorial H; *cis*-quinolizidine) 3-unsubstituted compounds, they are in general much closer to those of the normal series. When measured at shorter wave lengths (Figure 1), the rotations given by 3-methylyohimbone are seen to converge with those of yohimbone and eventually become more negative. If it could be assumed that the effect of a methyl group on the rotation is not too much different from that of a hydrogen, these data would suggest that the 3-methyl derivatives have the normal configuration with the methyl α and axial. This is the result which would be expected from a kinetically controlled mechanism involving least hindered attack (axial, *trans* to the axial C-14 hydrogen) by the methyllithium.[29] It would be

(22) Leonard and co-workers,[13a] have shown that the base derived from 5,10-dehydroquinolizidinium perchlorate was unreactive toward lithium aluminum hydride.

(23) Leonard and Hay[13b] attributed their results to steric factors which permit the Zerevitinov reaction to predominate completely.

(24) B. Witkop, *Ann.*, **554**, 83 (1943).

(25) 3-Unsubstituted yohimbanes of both the normal and the pseudo series are readily converted to the corresponding 3-dehydroyohimbane chlorides under these conditions.[10]

(26) The n.m.r. spectra were all determined in deuterated chloroform using the Varian Model A-60 spectrometer with tetramethylsilane as an internal standard.

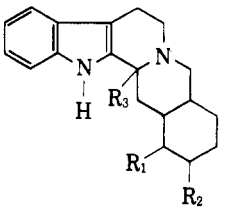
(27) W. E. Rosen and J. N. Shoolery [*J. Am. Chem. Soc.*, **83**, 4816 (1961)] have assigned a signal at 4.45 p.p.m. to the equatorial C-3 hydrogen of methyl reserpate. They reported that methyl isoreserpate, which has an axial C-3 hydrogen, gives no signal between 3.80 and 6.66 p.p.m.

(28) J. D. Albright, L. A. Mitscher, and L. Goldman [*J. Org. Chem.*, **28**, 38 (1963)] assigned a signal at 4.33 p.p.m. to the equatorial C-3 hydrogen of pseudoyohimbine when determined in deuterated dimethyl sulfoxide. We have found that in this solvent pseudoyohimbone gives a signal at 4.37 p.p.m. which is not given by yohimbone.

(29) F. Bohlmann, E. Winterfeldt, G. Boroschewski, R. Mayer-Mader, and B. Gatscheff [*Chem. Ber.*, **96**, 1792 (1963)] have proposed an analogous mechanism for the sodium borohydride reduction of 4-phenyl-4,10-dehydroquinolizidinium salts.

TABLE I

MOLECULAR ROTATIONS



		MD, (solvent)[a]				
R_1	R_2	R_3 = α-H	R_3 = CH_3	R_3 = $CH_2C_6H_5$	R_3 = C_6H_5	R_3 = β-H
H	H	−342 (py.)	−288	−14.8	−644	
		−238 (EtOH)[b]	−197			+173[a]
		−224 ($CHCl_3$)	−206	−710	−570	
H	=O	−344 (py.)[c]	−271			−70.6[g]
		−300 ($CHCl_3$)	−237			−167
H	β-OH	−311 (py.)	−248			−71.0[h]
		−213 (MeOH)[d]				
α-CH_3	α-OH	−71.3 (py.)[e]	+45.4			+352[i]
α-CH_3	=O	−314 (py.)[f]	−225			

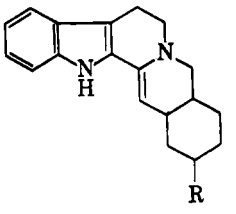
[a] All of the tabulated values were determined in these laboratories with the exception of that given for 3-epiyohimbane (pseudoyohimbane) which was obtained from ref. 2a. [b] Ref. 39 gives $[\alpha]D$ −82° or MD −230°. [c] Ref. 24 gives $[\alpha]D$ −105° or MD −309°. [d] Ref. 40 gives $[\alpha]D$ −72° or MD −213°. [e] Ref. 41b gives $[\alpha]D$ −20.4° or MD −63.2°. [f] Prepared by the method of J. Shavel, Jr., and M. von Strandtmann, U. S. Patent 3,096,245 (July 2, 1963); Z. J. Vejalek and K. Macek [*Chem. Listy*, **52**, 2140 (1958)] give $[\alpha]D$ −101° or MD −311°. [g] Ref. 5 gives $[\alpha]D$ −24° or MD −70.6°. [h] This (3-epi-17β-hydroxyyohimbane) is a previously unreported compound, the preparation of which (potassium borohydride reduction of pseudoyohimbone) is described in the Experimental section. [i] Unpublished results of M. von Strandtmann and J. Shavel, Jr.; the tabulated value is for the amorphous base; the crystalline perchlorate hemihydrate has $[\alpha]D$ +143° or MD +601° in pyridine.

analogous to sodium borohydride reduction of 3-dehydroyohimbane salts[9,10] which gives exclusively the normal product.[30]

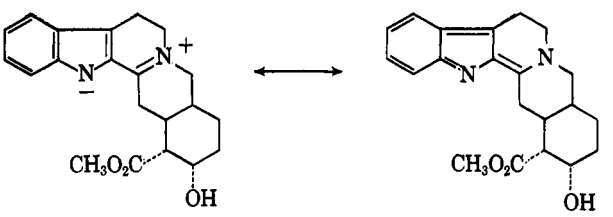
In the case of 3-phenylyohimbane, rotation values would be expected to be of little help in assigning configuration since a chromophore at an asymmetric center would be expected to exert an effect of its own. With 3-benzylyohimbane, the apparently anomalous rotations (if the configuration of the benzyl group is α) are more difficult to explain.[32]

An attempt to utilize the infrared absorption in the 2700–2800-cm.$^{-1}$ region.[2a,7,31] to confirm the α-configurational assignment gave inconclusive results. As can be seen from Figure 2, the spectra[33] of all of the 3-methylyohimbanes as well as that of 3-benzylyohimbane are different from that of pseudoyohimbone in that the former have broad absorption of medium intensity which extends below 2800 cm.$^{-1}$ and have a very weak band at 2715 cm.$^{-1}$ Nevertheless, we are hesitant to conclude that this is presumptive evidence for a *trans*-quinolizidine structure since they do not give the pattern of sharp, clearly resolved bands which is displayed by yohimbone. If the 3-methyl- and 3-benzylyohimbanes do have the *trans*-quinolizidine structure, this decreased resolution might be the result of there being one less hydrogen *trans* axial to the electron pair of the nitrogen. This is the explanation given by Bohlmann[31b] for the fact that the absorption of 10-methylquinolizidine in this region is less intense then that given by quinolizidine itself. Unlike 3-methylyohimbane, however, 10-methylquinolizidine does give fairly well-resolved bands.[34] 3-Phenylyohimbane appears to have the same type of absorption in this region as does pseudoyohimbone, suggesting that the former might be a *cis*-quinolizidine.

In the course of this work we prepared the previously unreported crystalline 3-dehydroyohimbane (Va) and 3-dehydro-17β-hydroxyyohimbane (Vb) bases by treatment of respective salts IIa and IIc with alkali. Com-



Va, R=H
b, R=OH



VI

(30) Among the 3-unsubstituted compounds, those belonging to the *trans*-fused normal series are clearly more stable than those of the *cis*-fused pseudo series. While it would be expected that nonbonded interactions of an axial substituent at position 3 would decrease the energy difference between the two forms, spectral studies have indicated[31b] that 10-methylquinolizidine exists primarily in the *trans* form. The assignment of the axial conformation to the 10-methyl group in 10-methylquinolizidine cannot be used as evidence for the same conformation in the 3-substituted yohimbanes even though their formation[12] undoubtedly takes place by similar mechanisms. With the nonrigid 10-methylquinolizidine, the conformation of the final product would be governed by equilibration to the most stable form rather than by kinetic control in the alkylation.

(31) (a) F. Bohlmann, *Angew. Chem.*, **69**, 641 (1957); (b) *Chem. Ber.*, **91**, 2157 (1958).

(32) Dreiding models of 3α-methylyohimbane and 3α-phenylyohimbane show the usual nonbonded interactions which are expected for axial substituents. However, with 3α-benzylyohimbane there is considerable hindrance to free rotation of the phenyl group which might be reflected in the anomalous rotation values.

(33) The spectra were determined in chloroform solutions using a calcium fluoride prism.

(34) Based on observation of the spectrum reproduced in ref. 31b.

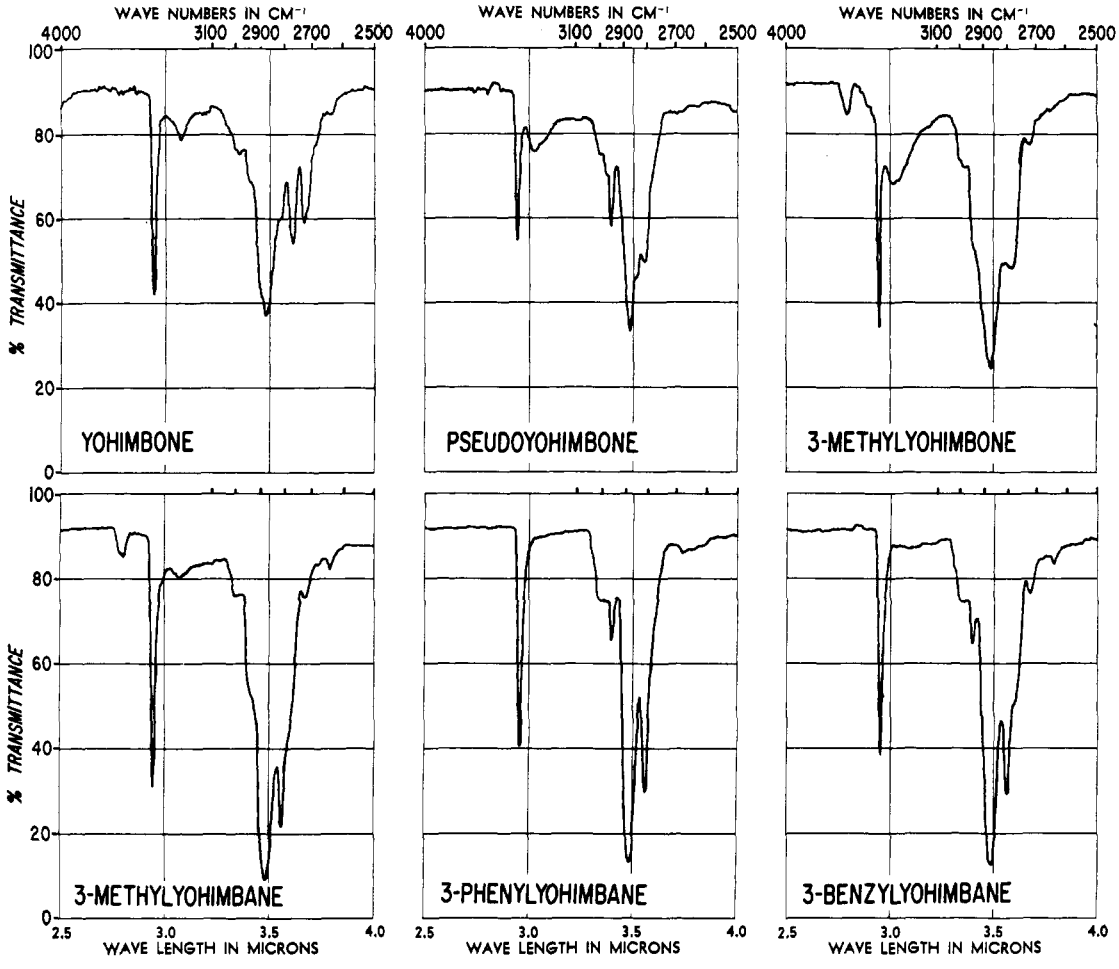


Figure 2.—Infrared spectra; C–H stretching region of yohimbanes.

pound Va is of interest in that its infrared spectrum was found to have a strong NH band at 3480 in chloroform solution and at 3400 cm.$^{-1}$ as a Nujol mull. This is evidence for structure V being the correct one for the 3-dehydroyohimbane bases as opposed to the hybrid structure VI proposed by Godtfredsen and Vangedal for 3-dehydroyohimbine.[35,36]

Experimental

Melting points were taken on a Mel-Temp hot stage in open capillaries and are uncorrected. Since most of the compounds studied decompose at a temperature considerably below the melting point, the products from successive recrystallizations were compared directly, the capillaries being placed in the apparatus about 10° below the melting point. Criteria for homogeneity of the analytical samples were recrystallization to constant optical rotation and a single spot on paper chromatography and paper ionophoresis.

Rotations were all taken in a 1-dm. tube, using a Rudolph Model 800 photoelectric polarimeter. The solvents and concentrations (per cent, w./v.) are given in parentheses. Rotations at the shorter wave lengths were determined with the same apparatus using a mercury lamp with appropriate filters.

Paper chromatographic analysis was carried out using the "Chromatobox"[37] technique. The compounds were spotted (as solutions in glacial acetic acid, aqueous acetic acid, chloroform, or methanol) on Whatman No. 1 paper; the paper was then impregnated by spraying with 10% formamide in acetone solution and allowed to air dry for about 2 min.; it was then placed in the "Chromatobox" and eluted while maintaining an ammonia atmosphere by placing a vial of concentrated aqueous ammonium hydroxide in the box. The eluents were a mixture of acetone, heptane, and benzene, in proportions of 1:1:1 and 1:2:1. Running time for the chromatograms was about 90 min. The spots were developed with potassium iodoplatinate. Paper ionophoresis was carried out at 600 v. using 5 *N* acetic acid containing 10% glycerin. Running time was 30–45 min., the spots being developed with potassium iodoplatinate.

The ultraviolet spectra were determined using a Beckmann DKI spectrophotometer. Unless otherwise stated the solvent was ordinary spectral grade 95% ethanol. Infrared spectra were recorded with a Baird Model 455 double beam instrument; the per cent absorption is given in parenthesis. In recording the latter values, the base line varied between 5–15% absorption. The values for per cent absorption are not to be construed as absolute measures of extinction but are given merely to call the reader's attention to the relative size of the peaks in a given spectrum without actually reproducing the curve.[38]

3-Dehydroyohimbane Chloride (IIa).[14]—From 49 g. (0.175 mole) of yohimbane[39] there was obtained 50 g. of product, m.p. 265–270° dec., $[\alpha]_D$ +106° (water, *c* 0.52). Recrystallization from acetonitrile gave material: m.p. 265–270° dec.; $[\alpha]_D$ +101° (water, *c* 0.65); ν_{max}^{Nujol} 3400 (66), 1634 (76), 1575 (61), 1552 cm.$^{-1}$ (88%); λ_{max} 246 mμ (ε 10,000), 352 (22,000); λ_{min} 228 mμ (ε 7000), 274 (250).

(35) The assignment of structure VI by Godtfredsen and Vangedal,[10] was possibly the result of erroneously concluding that 3-dehydroyohimbine base has no NH band when in effect this may have been fused with that resulting from the 17-hydroxy group. While we have not observed the spectrum of 3-dehydroyohimbine base, we can report that the NH and OH absorption of compound Vb appear as a single band at 3200 cm.$^{-1}$ when the spectrum is determined as a Nujol mull. Unfortunately the compound is too insoluble to permit recording of a solution spectrum.

(36) Stork and Hill,[12] assigned structure Va to 3-dehydroalloyohimbane, which was an unpurified intermediate in their total synthesis of *dl*-alloyohimbane and *dl*-3-epialloyohimbane.

(37) J. Barrollier, *Naturwiss.*, **42**, 786 (1955).

(38) This method of presenting spectra has been used by J. C. Seaton; M. D. Nair, O. E. Edwards, and L. Marion [*Can. J. Chem.*, **38**, 1035 (1960)].

(39) J. Jost, *Helv. Chim. Acta*, **32**, 1297 (1949).

Anal. Calcd. for $C_{19}H_{22}ClN_2$: C, 72.24; H, 7.65; N, 8.87. Found: C, 72.15; H, 7.49; N, 8.80.

3-Dehydro-17β-hydroxyyohimbane Chloride (IIc).[14]—From 85.8 g. (0.29 mole) of 17β-hydroxyyohimbane[40] there was obtained a crude product which was dissolved in 300 ml. of hot methanol, the solution was filtered, and 900 ml. of isopropyl alcohol was added. Distillation was carried out at atmospheric pressure until crystals separated and the mixture was allowed to stand at room temperature. The crystals were collected and combined with a second crop obtained by further concentration and cooling to give a total of 56.6 g. of material, m.p. 297–300° dec., $[\alpha]_D$ +88° (water, *c* 0.50). Recrystallization from the same solvent combination gave material, m.p. 298–301° dec., $[\alpha]_D$ +82° (water, *c* 0.60).

Anal. Calcd. for $C_{19}H_{23}ClN_2O$: C, 68.97; H, 7.01; Cl, 10.72; N, 8.47. Found: C, 68.77; H, 6.96; Cl, 10.58; N, 8.50.

3-Dehydro-16α-methyl-17α-hydroxyyohimbane Chloride (IId).[14]—From 31 g. (0.1 mole) of 16α-methyl-17α-hydroxyyohimbane[41] there was obtained 26 g. of product, m.p. 290–294° dec., $[\alpha]_D$ +187° (water, *c* 0.60). Recrystallization of a portion from ethanol gave material, m.p. 287–290° dec., $[\alpha]_D$ +193° (water, *c* 0.57).

Anal. Calcd. for $C_{20}H_{25}ClN_2O$: C, 69.65; H, 7.31; Cl, 10.28; N, 8.12. Found: C, 69.54; H, 7.41; Cl, 10.46; N, 7.94.

3-Dehydroyohimbane Base (Va).—A solution of 6.3 g. of 3-dehydroyohimbane chloride in 100 ml. of water was made strongly basic with sodium hydroxide and the mixture was extracted with methylene chloride. The methylene chloride solution was dried over sodium sulfate and was distilled *in vacuo* to dryness. The residue was recrystallized from methanol to give 1.8 g. of product, $[\alpha]_D$ +28° (pyridine, *c* 0.60). Considerable decomposition appeared to take place during recrystallization since further concentration of the mother liquor in an attempt to obtain more crystals gave only a reddish black gum. The crystalline product was recrystallized again from methanol to give material which started to darken at 135° and slowly decomposed to a black mass at 145°: $[\alpha]_D$ +28° (pyridine, *c* 0.59); $\nu_{max}^{CHCl_3}$ 3470 (57), 1640 cm.$^{-1}$ (47%); ν_{max}^{Nujol} 3400 (65), 1636 (37), 746 (68), and 740 cm.$^{-1}$ (70%); $\lambda_{max}^{neut\ 95\%\ EtOH}$ 229–231 (ε 24,500), 258 sh (8500), 295 sh (17,500), 306 (22,200), and 317–318 (20,000); λ_{min} 267 mμ (ε 6400), 314 (19,000); $\lambda_{max}^{CH_2Cl_2}$ 233–235 mμ (ε 19,900), 305 (15,200), and 311–312 sh (14,800); λ_{min} 266 mμ (ε 5700); $\lambda_{max}^{CH_3CN}$ 227 mμ (ε 32,400), 273–274 (7300), 280 (7500), 289 (6500), and 320 (2700); λ_{min} 247 mμ (ε 4500), 276 (7200), 286 (6000), and 308–310 (2500).[42]

Anal. Calcd. for $C_{19}H_{22}N_2$: C, 81.97; H, 7.97; N, 10.06. Found: C, 81.97; H, 8.04; N, 9.95.

3-Dehydro-17β-hydroxyyohimbane Base (Vb).—A solution of 1 g. of 3-dehydro-17β-hydroxyyohimbane chloride in 50 ml. of water was made strongly alkaline with sodium hydroxide. The precipitated solid was collected, washed well with water, sucked dry, and recrystallized from methanol to give 0.6 g. of product, m.p. 209–213° dec., $[\alpha]_D$ +68° (pyridine, *c* 0.75). Recrystallization from methanol gave material: m.p. 212–215° dec.; $[\alpha]_D$ +69° (pyridine, *c* 0.84); ν_{max}^{Nujol} 3200 (74), 1647 (34), and 746 cm.$^{-1}$ (77%); $\lambda_{max}^{neut\ 95\%\ EtOH}$ 230 mμ (ε 24,000), 260 sh (8000), 296 sh (17,100), 306–307 (21,500), and 318 (19,400); λ_{min} 267 mμ (ε 6000) and 314 (18,500).

Anal. Calcd. for $C_{19}H_{22}N_2O$: C, 77.51; H, 7.53; N, 9.51. Found: C, 77.41; H, 7.62; N, 9.81.

3ξ-Cyanoyohimbine (Ib).—To a stirred solution of 7.8 g. of 3-dehydroyohimbine chloride in 200 ml. of 50% aqueous methanol at room temperature was added a solution of 4 g. of potassium cyanide in 100 ml. of 50% aqueous methanol. The mixture was stirred for 30 min. and allowed to stand at room temperature for 1 hr. The resulting crystalline precipitate was collected by filtration, washed with two 50-ml. portions of 50% aqueous methanol followed by 50 ml. of absolute methanol, and air dried. It was recrystallized from acetonitrile and dried *in vacuo* at 80° for 2 hr. to yield 4.6 g. of material which darkened at 152°, and slowly decomposed and melted with decomposition at 175–185°, $[\alpha]_D$ +44° (pyridine, *c* 0.63). Another recrystallization from acetonitrile gave material which darkened at 154°, slowly decomposed, and melted with decomposition at 178–185°, $[\alpha]_D$ +47° (pyridine, *c* 0.60) and $[\alpha]_D$ −27° (chloroform, *c* 0.51); ν_{max}^{Nujol} 3440 (83), 3240 (79), 2300 (15), and 1732 cm.$^{-1}$ (91%); $\lambda_{max}^{CH_2Cl_2}$ 283 mμ (ε 8700), 291 (9000), 303–306 (8800), and 314–317 (8400); λ_{min} 258–259 mμ (ε 6100), 285 (8000), and 298 (8000); $\lambda_{max}^{neut\ 95\%\ EtOH}$ 228 mμ (ε 24,200), 257 sh (8500), 295 sh (18,000), 307 (22,800), and 318 (20,000); λ_{min} 266 mμ (ε 6300) and 314 (19,500); $\lambda_{max}^{CH_3CN}$ 223 mμ (ε 29,200), 282 (7800), 289 (8000), 305–308 (6000), and 317–318 (6100); λ_{min} 256 mμ (ε 5200), 286–287 (7400), and 298 (5600).

Anal. Calcd. for $C_{22}H_{25}N_3O_3$: C, 69.63; H, 6.64; N, 11.08. Found: C, 69.91; H, 6.79; N, 10.84.

3ξ-Cyanoyohimbane (Ia).—To a stirred solution of 15.8 g. of 3-dehydroyohimbane chloride in 400 ml. of 50% aqueous methanol at room temperature was added a solution of 8 g. of potassium cyanide in 50 ml. of 50% aqueous methanol. The mixture was stirred for 15 min. and then allowed to stand at room temperature for 1 hr. The resulting crystalline precipitate was collected by filtration, washed with two 50-ml. portions of 50% aqueous methanol followed by 50 ml. of absolute methanol, and then dried *in vacuo* at 60° for 4 hr. The yield of Ia was 14.8 g., $[\alpha]_D$ −122° (pyridine *c* 0.65); the compound darkened at 95° and slowly decomposed and melted with decomposition at 145–160°. This material was sufficiently pure to be used as an intermediate in further reactions. A portion was recrystallized from methanol to give material which darkened at 100°, slowly decomposed and melted with decomposition at 145–160°, $[\alpha]_D$ −129° (pyridine, *c* 0.61) and $[\alpha]_D$ −92° (chloroform, *c* 0.52); ν_{max}^{Nujol} 3320 (79) and 2300 cm.$^{-1}$ (15%); $\nu_{max}^{CH_2Cl_2}$ 3440 (92) and 2300 cm.$^{-1}$ (80%); $\lambda_{max}^{CH_3CN}$ 223 mμ (ε 29,500), 282 (7500), 290 (7250), 305–312 (4700), and 318 (5000); λ_{min} 256 mμ (ε 5000), 287 (6750), and 300 (4500).

Anal. Calcd. for $C_{20}H_{23}N_3$: C, 78.65; H, 7.59; N, 13.76. Found: C, 78.43; H, 7.82; N, 13.52.

3ξ-Methylyohimbane (IIIa). A. From 3-Dehydroyohimbane Perchlorate (IIa).—A mixture of 11.4 g. (0.03 mole) of 3-dehydroyohimbane perchlorate[9] and 0.25 mole of methyllithium in 250 ml. of ether was refluxed with stirring for 7 hr. The mixture was poured on ice–water, the layers were separated, and the aqueous layer was extracted with ether. The dried (sodium sulfate) ether solution was evaporated to give an oil which on trituration with 50 ml. of methanol yielded 2.4 g. of crystalline product, m.p. 127–130° (softened at 90°), $[\alpha]_D$ −92° (pyridine, *c* 0.65), which gave a single spot on ionophoresis and paper chromatography and whose ultraviolet spectrum (in acidified ethanol) showed complete absence of 3-dehydroyohimbane. Recrystallization from methanol gave material (dried *in vacuo* at 80°), m.p. 130–132° (softened at 90°), $[\alpha]_D$ −91° (pyridine, *c* 0.62), $[\alpha]_D$ −64° (chloroform, *c* 0.55), and $[\alpha]_D$ −62° (ethanol, *c* 0.60).

Anal. Calcd. for $C_{20}H_{26}N_2 \cdot CH_3OH$: C, 77.25; H, 9.26; N, 8.58. Found: C, 77.04; H, 9.15; N, 8.32.

A sample was dried *in vacuo* at 110° for 8 hr. to give material, m.p. 130–132°, $[\alpha]_D$ −98° (pyridine, *c* 0.65), $[\alpha]_D$ −70° (chloroform, *c* 0.62), and $[\alpha]_D$ −67° (ethanol, *c* 0.59); pK_A' 7.93 (70% ethanol); yohimbane had pK_A' 7.46 in the same system; ν_{max}^{Nujol} 3420 (57), 3270 (58), 752 (63), and 746 cm.$^{-1}$ (67%); $\nu_{max}^{CHCl_3}$ 3470 (44) and 1294 cm.$^{-1}$ (63%); λ_{max} 225 mμ (ε 36,600), 272 sh (7250), 279–282 (7500), and 289 (6400); λ_{min} 245 mμ (ε 2200) and 286 (6300).

Anal. Calcd. for $C_{20}H_{26}N_2$: C, 81.58; H, 8.90; N, 9.52; C-methyl, 5.11. Found: C, 81.83; H, 9.04; N, 9.73; C-methyl, 4.13.

B. From 3ξ-Cyanoyohimbane (Ia).—To a solution of 0.5 mole of methyllithium in 375 ml. of ether was added a solution of 15.3 g. (0.05 mole) of 3ξ-cyanoyohimbane in 200 ml. of dry benzene. An additional 550 ml. of benzene was added and the mixture was refluxed with stirring for 8 hr., the reflux temperature being 56°. It was poured on ice–water, the layers were separated, and the aqueous layer was extracted with three 200-ml. portions of ether. The combined organic layers were washed with 30 ml. of water and then extracted with five 250-ml. portions of 15% aqueous acetic acid. The acetic acid solution was made basic with ammonium hydroxide and the resulting precipitate was collected by

(40) A. Chatterjee and S. Ghosal, *J. Ind. Chem. Soc.*, **36**, 545 (1959).

(41) (a) P. Karrer and R. Seamann, *Helv. Chim. Acta*, **35**, 1932 (1952); (b) R. C. Elderfield, A. E. Hydron, E. Schenker, and K. K. Wyckoff, *J. Org. Chem.*, **24**, 1296 (1959).

(42) Ref. 10 reports essentially the same ultraviolet spectrum for 3-dehydroyohimbine base in ethanol. We have found that the spectrum obtained in ordinary spectral grade ethanol always displayed a considerable amount of the absorption at 352 mμ which is characteristic for 3-dehydroyohimbane salts. Thus it was necessary to neutralize the ethanol with a few drops of dilute aqueous sodium hydroxide in order to obtain the spectrum of the pure dehydro base. Conversion of dehydro bases to salts in a very slightly acidic solution is not unexpected since the former are extremely strong bases. Leonard, *et al.*,[12a] reported the pK_A' of 5,10-dehydroquinolizidinium perchlorate to be 11.1 when determined in 66% dimethylformamide.

filtration, washed with water, air dried, recrystallized from 50 ml. of methanol, and dried *in vacuo* at 80° to give 6.6 g. of product, m.p. 127–130° (softened at 90°), $[\alpha]_D$ −91° (pyridine, *c* 0.54) which gave a single spot on ionophoresis and paper chromatography corresponding exactly with that given by 3ξ-methylyohimbane prepared from 3-dehydroyohimbane perchlorate. The ultraviolet spectrum in acidified ethanol solution showed complete absence of the maximum at 352 mμ which is characteristic of 3-dehydroyohimbane salts. The amorphous residue obtained on evaporation of the methanol filtrate appeared from its ionogram and ultraviolet spectrum to consist of approximately equal amounts of 3ξ-methylyohimbane and 3-dehydroyohimbane.

3ξ-Phenylyohimbane (IIIb). A. From 3-Dehydroyohimbane Perchlorate (IIa).—A mixture of 11.4 g. (0.03 mole) of 3-dehydroyohimbane perchlorate and 0.3 mole of phenyllithium in 400 ml. of ether was refluxed with stirring for 19 hr. The reaction mixture was poured on ice–water, the layers were separated, and the aqueous layer was extracted with ether. The combined ether solutions were dried over sodium sulfate and were treated with ethereal hydrogen bromide. The first material to precipitate was collected and recrystallized from acetone to give 1.7 g. of yellow crystals which could be shown by ionophoresis and ultraviolet spectrum to be 3-dehydroyohimbane bromide. On the addition of more ethereal hydrogen bromide there was obtained a dark green gum which solidified on trituration with water. The solid was recrystallized once from acetonitrile and once from methanol to give 1.3 g. of 3-phenylyohimbane hydrobromide hemimethanolate, m.p. 287–294° dec. (started to darken at *ca.* 220°).

Anal. Calcd. for $C_{25}H_{29}BrN_2 \cdot 0.5CH_3OH$: C, 67.54; H, 6.89; Br, 17.63; N, 6.18. Found: C, 67.84; H, 6.79; Br, 17.68; N, 5.89.

A suspension of 700 mg. of the recrystallized hydrobromide in an excess of aqueous ammonium hydroxide was shaken with methylene chloride. The methylene chloride solution was dried over sodium sulfate and distilled to dryness to give a residue which was recrystallized from methanol to give 400 mg. of 3-phenylyohimbane base, m.p. 237–240° dec., $[\alpha]_D$ −179° (pyridine, *c* 0.62).

The acetonitrile and methanol filtrates from the hydrobromide recrystallization were evaporated to dryness, the residue was dissolved in 100 ml. of methanol, and an excess of aqueous ammonium hydroxide was added. A small amount of dark insoluble material was filtered off, the solution was heated to boiling, and 90 ml. of water was added. The yellow precipitate which separated on cooling to room temperature was collected by filtration, washed with water, dried, and recrystallized from methanol to give 1.5 g. of 3-phenylyohimbane base, m.p. 235–239° dec., $[\alpha]_D$ −177° (pyridine, *c* 0.57). Recrystallization from methanol gave material: m.p. 238–241° dec. (started to darken at 197°); $[\alpha]_D$ −181° (pyridine, *c* 0.54) and $[\alpha]_D$ −160° (chloroform, *c* 0.51); pK_A' 6.40 (70% ethanol); ν_{max}^{Nujol} 3420 (66), 746 (89), and 706 cm.$^{-1}$ (86%); $\nu_{max}^{CHCl_3}$ 3420 (75), 1618 (29), 1597 (42), 1292 (89), and 983 cm.$^{-1}$ (84%); λ_{max} 228 mμ (ε 38,500), 284 (9750), and 291 (8750); λ_{min} 251–252 mμ (ε 3800) and 289 (8500).

Anal. Calcd. for $C_{25}H_{28}N_2$: C, 84.22; H, 7.92; N, 7.86. Found: C, 84.43; H, 8.12; N, 8.03.

B. From 3ξ-Cyanoyohimbane (Ia).—To 0.5 mole of phenyllithium in 400 ml. of ether was added a solution of 15.3 g. (0.05 mole) of 3ξ-cyanoyohimbane in 800 ml. of benzene and the mixture was refluxed with stirring for 10 hr. It was poured on ice–water, the layers were separated, and the aqueous layer was extracted with ether. The combined organic layers were extracted with five 200-ml. portions of 20% aqueous acetic acid, washed with two portions of aqueous ammonium hydroxide, dried over sodium sulfate, and distilled to dryness. The residue was triturated with 30 ml. of methanol to give 4.7 g. of crystals, m.p. 235–238° dec., $[\alpha]_D$ −176° (pyridine, *c* 0.65), which gave a single spot on ionophoresis and paper chromatography and whose ultraviolet spectrum showed them to be free of 3-dehydroyohimbane.

3ξ-Methyl-17β-hydroxyyohimbane (IIIc).—A mixture of 33 g. (0.1 mole) of 3-dehydro-17β-hydroxyyohimbane chloride (IIc), 1 mole of methyllithium, 875 ml. of ether, and 2000 ml. of dry benzene was refluxed with stirring for 20 hr. It was poured on ice–water, the layers were separated, and the aqueous layer was extracted with ether. An insoluble solid which remained at the interface was collected by filtration. It weighed 4.1 g. and was shown by ionophoresis and paper chromatography to consist entirely of 3-dehydro-17β-hydroxyyohimbane base. The combined organic layers were dried over sodium sulfate and distilled at atmospheric pressure until the resulting mixture began to bump. It was filtered while hot to give 3.7 g. of crystalline material which was also shown to consist wholly of 3-dehydro-17β-hydroxyyohimbane base. The filtrate (which began to deposit crystals on cooling) was extracted with 15% acetic acid, and the aqueous solution was made basic with ammonium hydroxide. The resulting precipitate was filtered off, washed with water, and sucked dry. Ionophoresis and paper chromatography showed it to be almost free of the starting 3-dehydro compound. It was dried by azeotropically distilling with benzene and was triturated with 25 ml. of methanol to give 11.4 g. of product, m.p. 136–138° (gas evolution and darkening), $[\alpha]_D$ −75° (pyridine, *c* 0.62). Recrystallization from methanol gave material (dried *in vacuo* at 110° for 16 hr.), m.p. 139–142° (gas evolution), $[\alpha]_D$ −73° (pyridine, *c* 0.60).

Anal. Calcd. for $C_{20}H_{26}N_2O \cdot 0.5CH_3OH$: C, 75.51; H, 8.64. Found: C, 75.58; H, 8.60.

A sample was dried *in vacuo* at 140° for 3 hr., m.p. 144–148°, $[\alpha]_D$ −80° (pyridine, *c* 0.73).

Anal. Calcd. for $C_{20}H_{26}N_2O$: C, 77.38; H, 8.44; N, 9.02. Found: C, 77.10; H, 8.66; N, 8.99.

The two crops of 3-dehydro-17β-hydroxyyohimbane base were combined and recrystallized from methanol to give 5.4 g. of material, $[\alpha]_D$ +69° (pyridine, *c* 0.60).

3ξ,16α-Dimethyl-17α-hydroxyyohimbane (IIId).—A mixture of 16.5 g. (0.05 mole) of 3-dehydro-16α-methyl-17α-hydroxyyohimbane chloride (IId), 0.5 mole methyllithium, 400 ml. of ether, and 900 ml. of benzene was refluxed with stirring for 7 hr. It was poured on ice–water, the layers were separated, and the aqueous layer was extracted with ether. The combined organic layers were washed with water, extracted with five 200-ml. portions of 15% acetic acid, and the acetic acid solution was basified with ammonium hydroxide. The resulting precipitate was filtered off, washed with water, dried, and recrystallized twice from ethyl acetate to give 5.5 g. of product, m.p. 206–213° dec. (darkened at 195°), $[\alpha]_D$ +14° (pyridine, *c* 0.61). Recrystallization from the same solvent gave material, m.p. 211–222° dec., $[\alpha]_D$ +14° (pyridine, *c* 0.61).

Anal. Calcd. for $C_{21}H_{28}N_2O$: C, 77.74; H, 8.70; N, 8.64. Found: C, 77.95; H, 8.56; N, 8.84.

3ξ,16α-Dimethylyohimbone (IVb).—A mixture of 8.8 g. (0.027 mole) of 3ξ,16α-dimethyl-17α-hydroxyyohimbane (IIId), 550 ml. of xylene, and 220 ml. of cyclohexanone was distilled at atmospheric pressure until 100 ml. of distillate was collected. It was cooled to room temperature, 39 g. of aluminum phenoxide was added, and it was refluxed with stirring for 24 hr. The reaction mixture was cooled to room temperature and was extracted with three 275-ml. portions of 40% potassium hydroxide. The organic layer was extracted with five 250-ml. portions of 15% acetic acid; the aqueous solution was made strongly basic with ammonium hydroxide and extracted with chloroform. The dried (sodium sulfate) chloroform solution was distilled *in vacuo* to give an oil which solidified on trituration with petroleum ether. This solid was collected and recrystallized from methanol to give 5.0 g. of product, m.p. 255–260° dec., $[\alpha]_D$ −69° (pyridine, *c* 0.83). Recrystallization from methanol gave material: m.p. 255–260° dec.; $[\alpha]_D$ −70° (pyridine, *c* 0.60); ν_{max}^{Nujol} 3450 (70), 1696 (80), and 744 cm.$^{-1}$ (70%).

Anal. Calcd. for $C_{21}H_{26}N_2O$: C, 78.22; H, 8.13; N, 8.69. Found: C, 78.45; H, 8.22; N, 8.76.

3ξ-Methylyohimbone (IVa).—A mixture of 6.2 g. (0.02 mole) of 3ξ-methyl-17β-hydroxyyohimbane (IIIc), 300 ml. of dry benzene, and 150 ml. of cyclohexanone (previously dried over sodium sulfate) was distilled at atmospheric pressure until 30 ml. of distillate was collected. The mixture was cooled to room temperature and, after addition of 26 g. of aluminum phenoxide, it was refluxed for 53 hr. after which a paper chromatogram showed that only about 75% conversion had taken place. The reaction mixture was extracted with three 200-ml. portions of 40% potassium hydroxide followed by four 100-ml. portions of 15% acetic acid. The acetic acid solution was made basic with ammonium hydroxide and the resulting solid was collected by filtration. It was dissolved in chloroform and the solution after drying over sodium sulfate was concentrated to a volume of about 150 ml. This was chromatographed over a Florisil column (55 g.) using chloroform as the eluent. The first 300 ml. of eluate was evaporated to dryness to yield 2.3 g. of material, m.p. 152–157° dec., $[\alpha]_D$ −86° (pyridine, *c* 0.53), whose chromatogram showed it to be completely free of the starting alcohol. Recrystallization from acetonitrile gave material, m.p. 170–172° dec., $[\alpha]_D$ −88° (pyri-

dine, *c* 0.74) and $[\alpha]_D$ −81° (chloroform, *c* 0.57); O.R.D. in chloroform (*c* 0.205): $[\alpha]_{578}$ −78.2°, $[\alpha]_{546}$ −91.1°, $[\alpha]_{435}$ −190, $[\alpha]_{405}$ −284°, and $[\alpha]_{365}$ −485°[43]; ν_{max}^{Nujol} 3430 (72), 1706 (88), and 749 cm.$^{-1}$ (90%).

Anal. Calcd. for $C_{20}H_{24}N_2O$: C, 77.88; H, 7.84; N, 9.08. Found: C, 77.80; H, 7.92; N, 9.20.

Further elution of the column with chloroform followed by chloroform containing 1 and 5% methanol, respectively, yielded 1.75 g. of the starting alcohol as was shown by its paper chromatogram and infrared spectrum.

3ξ-Benzylyohimbane (IIIe).—Benzylmagnesium bromide was prepared by dropwise addition of a solution of 34 g. of benzyl bromide in 400 ml. ether to a stirred suspension of 15.8 g. of magnesium in 100 ml. of ether. When addition was completed the mixture was stirred at room temperature for 1 hr. longer and then refluxed for 45 min. To the Grignard reagent was added 12 g. (0.038 mole) of 3-dehydroyohimbane chloride (IIa). The reaction mixture was stirred at room temperature for 4 hr., allowed to stand at room temperature overnight, and was then poured into a solution of 30 g. of ammonium chloride in 600 ml. of ice water. After separation of the layers, the aqueous layer was extracted with several portions of ether, the combined ether solutions were dried over sodium sulfate, and were evaporated to dryness. The residue was dissolved in 200 ml. of 50% acetic acid, water was added to reduce the acetic acid concentration to 15%, and partial neutralization to pH 4 was carried out by the addition of ammonium hydroxide. The aqueous solution was decanted from the gum which formed and the latter was dissolved in methylene chloride. This solution was dried over sodium sulfate, evaporated to dryness, and the residue was crystallized from methanol to give 6.7 g. of product, m.p. 221–222° dec., $[\alpha]_D$ −193° (chloroform, *c* 0.55). In addition there was obtained 0.8 g. of a second crop, m.p. 214–216° dec., $[\alpha]_D$ −199° (chloroform, *c* 0.54). Recrystallization of the first crop from methanol gave material: m.p. 222–223° dec.; $[\alpha]_D$ −192° (chloroform, *c* 0.56) and $[\alpha]_D$ −4° (pyridine, *c* 0.51); pK_A' (70% ethanol) 6.65; ν_{max}^{Nujol} 3420 (56), 1600 (23), 760 (50), 740 (79), and 730 cm.$^{-1}$ (50%); λ_{max} 225 mμ (ε 39,000), 275 sh (7500), 282–283 (8000), and 240 (7000); λ_{min} 253 mμ (ε 3500) and 288 (6800).

Anal. Calcd. for $C_{26}H_{30}N_2$: C, 84.28; H, 8.16; N, 7.56. Found: C, 84.05; H, 8.29; N, 7.76.

Attempted Reaction of 3-Dehydroyohimbane Base (Va) with Methyllithium.—A mixture of 150 mg. of 3-dehydroyohimbane base, 0.025 mole of methyllithium in 20 ml. of ether, and 15 ml. of benzene was refluxed with stirring for 24 hr. The reaction mixture was poured on ice–water, the layers were separated, and the aqueous layer was extracted with ether. The combined organic layers were dried over sodium sulfate and evaporated to dryness. Ionophoresis on the gummy residue showed only the spot corresponding to 3-dehydroyohimbane with the slower spot characteristic of 3ξ-methylyohimbane absent. Ionograms after the same reaction was carried out with 3-dehydroyohimbane chloride or perchlorate always showed, quite prominently, this slower spot.

Attempted Reaction of 3-Dehydro-17β-hydroxyyohimbane (Vb) with Methyllithium.—A mixture of 500 mg. of 3-dehydro-17β-hydroxyyohimbane base, 0.1 mole of methyllithium in 75 ml. of ether, and 30 ml. of benzene was refluxed for 24 hr. The reaction mixture was poured into ice–water, the layers were separated, and the aqueous layer was extracted with several portions of ether. The combined organic layers were dried over sodium sulfate and evaporated to dryness. Ionophoresis of the residue showed only the spot corresponding to 3-dehydro-17β-hydroxyyohimbane with the slower spot characteristic of 3ξ-methyl-17β-hydroxyyohimbane absent. Ionograms after the same reaction was carried out with 3-dehydro-17β-hydroxyyohimbane chloride always showed, quite prominently, this slower spot.

17β-Hydroxy-3-epiyohimbane.—A mixture of 1.5 g. (0.05 mole) of 3-epiyohimbone,[5] 1.0 g. of potassium borohydride, and 100 ml. of methanol was stirred at room temperature for 18 hr. Most of the methanol was removed by distillation *in vacuo* and the residue was partitioned between water and methylene chloride. The methylene chloride solution was dried over sodium sulfate and concentrated to a small volume whereupon crystals separated. These were collected and recrystallized from acetonitrile to give 0.8 g. of product: m.p. 178–180° dec.; $[\alpha]_D$ −24° (pyridine, *c* 0.55); ν_{max}^{Nujol} 3400 (57), 3160 (69), and 738 cm.$^{-1}$ (81%).

Anal. Calcd. for $C_{19}H_{24}N_2O$: C, 76.99; H, 8.16; N, 9.45. Found: C, 76.81; H, 8.30; N, 9.21.

***t*-Butyl Hypochlorite Oxidation of Yohimbane, 3ξ-Methylyohimbane (IIIa), 3ξ-Phenylyohimbane (IIIb), and 3ξ-Benzylyohimbane (IIIe).**—Solutions of 0.0005 mole of each of these compounds in a mixture of 60 mg. (0.06 mole) of triethylamine and 15 ml. of methylene chloride were cooled to −5°. To each flask was added a solution of 75 mg. (0.069 mole) of *t*-butyl hypochlorite in 1 ml. of methylene chloride. The reaction mixtures were allowed to stand at −5 to 0° for 20 min. and the resulting solutions were washed with two 10-ml. portions of water. The organic layers were dried over sodium sulfate and evaporated *in vacuo* to give residues which were dissolved in 10 ml. of 0.8 *N* ethanolic hydrogen chloride. Appropriate dilutions of these solutions were used for the determination of the ultraviolet spectra. It was found that only the product derived from yohimbane gave a strong maximum at 350 mμ. The other products were devoid of absorption in this region.

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(43) O.R.D. of yohimbone in chloroform (*c* 0.209): $[\alpha]_{578}$ −94.7°, $[\alpha]_{546}$ −106°, $[\alpha]_{435}$ −201°, $[\alpha]_{405}$ −281°, and $[\alpha]_{365}$ −440°. O.R.D. of pseudoyohimbone in chloroform (*c* 0.209): $[\alpha]_{578}$ −34.9°, $[\alpha]_{546}$ −47.9°, $[\alpha]_{435}$ −129°, $[\alpha]_{405}$ −213°, and $[\alpha]_{365}$ −398°.

Fonsecin, a Pigment from an *Aspergillus fonsecaeus* Mutant

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Fonsecin, a yellow pigment produced by an ultraviolet mutant of the fungus *Aspergillus fonsecaeus*, is shown to be the previously unknown 2-methyl-2,5,8-trihydroxy-6-methoxy-2,3-dihydro-4H-naphtho[2,3-*b*]pyran-4-one (I).

Aspergillus fonsecaeus, a fungus closely related to *A. niger*, normally produces a brown-black pigment.[3] In 1953 Raper and Fennell[4] reported that a number of lighter colored mutants could be obtained from *A. fonsecaeus* subjected to ultraviolet radiation. One of these mutants (O 16–1) is bright yellow and grows well on various substrata. It is, however, very short lived,

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